## REMARKS

1. **Amendments to the Specification to Correct Typographical Errors:**

Applicant has amended the specification to correct typographical errors discovered after filing. No new matter has been introduced.

2. **Claims Rejected Under 35 U.S.C. §102(b):**

The Examiner has rejected claims 1, 12, 13, 15-21, 29 and 38-45 under 35 U.S.C. § 102(b) as anticipated by *Czernielewski*. Claim16 has been withdrawn. Claims 1, 13, 15 and 38 have been amended. Claims, 12, 17-21, 29 and 39-45 remain as originally filed. Applicant respectfully contends that the remaining claims, as amended, should be allowed in light of the following arguments:

A. The Scope of *Czernielewski* is Restricted to Combinations of Metronidazole and Clindamycin:

The scope of *Czernielewski*, through its prosecution history, has clearly been restricted to cover only compounds including a combination of metronidazole and clindamycin, not metronidazole alone. Although there are claims present in *Czernielewski* which cover compounds including only metronidazole, it is absolutely unambiguous from a review of the file wrapper that the inventor in *Czernielewski* limited his claims to only combinations of metronidazole and clindamycin.

To wit, during prosecution of *Czernielewski* the examiner refused to allow claims directed at compounds with only metronidazole as the active ingredient (See Office Action dated June 3, 1997, Exhibit "A" hereto, at page 2 ) as being anticipated under 102(b). In response to this rejection, the inventor amended his claims and, in his remarks states unambiguously that:

> [u]pon entry of the subject amendments, **all of the claims** will be directed to a method for treating inflammation comprising administering a composition

comprising an effective amount of **metronidazole and clindamycin** in combination with a pharmaceutically acceptable carrier.

and:

[t]his rejection is moot as a topical composition containing metronidazole is no longer claimed

[See Response to Office Action dated December 3, 1997, Exhibit "B" hereto, at pages 4 and 8]

Inexplicably, however, the applicant submitted claims with metronidazole as the sole ingredient. Even more inexplicably, the examiner allowed those claims to issue. Outside of those claims, there is practically no support in the specification for compositions including only metronidazole. The specification is devoted almost entirely to the synergistic effects of metronidazole and clindamycin.

Accordingly, it is Applicant's position that *Czernielewski* covers only combinations of metronidazole and clindamycin and that the claims covering metronidazole alone were erroneously allowed and should not be grounds for a refusal under 35 U.S.C. § 102(b).

B. *Czernielewski* Does Not Disclose a Stable Formulation for the Use of Metronidazole in an Impregnated Inert Support:

Even if the scope of *Czernielewski* were deemed to cover the disclosed invention, *Czernielewski* does not disclose a formulation for a solution of metronidazole capable of being used in an impregnated inert support.

The compositions described in *Czernielewski* are impossible to apply using an impregnated inert support. *Czernielewski* describes two different compositions (Examples 2 and 3) which are for a cream and a gel. It would be obvious to an individual with reasonable skill in the relevant art that a pledget or pad, cannot, as a practical matter, be impregnated with a gel or a cream. Use of a solution is the only viable method for doing so. *Czernielewski* does not describe a solution of metronidazole alone or even in combination with clindamycin. Instead, it erroneously implies that the compositions it describes (i.e., a gel or a cream) can be infused into an "impregnated pad" without offering any support sufficient to enable such an application.

The invention claimed by Applicant requires use of an inert support and goes through extremely detailed description of such inert support. The only mention of anything even remotely resembling an inert support in *Czernielewski* is the passing mention of an "impregnated pad" among 11 possible delivery mechanisms for the compositions it describes without providing any detail about the "impregnated pads" being inert, much less describing materials which would render such "impregnated pads" inert in the presence of metronidazole and a major solvent.

Accordingly, *Czernielewski* does not describe all of the elements of the invention disclosed in the present invention and the Examiner's refusal under 35 U.S.C. § 102(b) should be withdrawn.

Notwithstanding the foregoing arguments, Applicant has amended the relevant claims to more specifically include the materials utilized in the inert support, the concentration of metronidazole in the solution and the composition of the major solvent used in the solution.

For the foregoing reason, and in view of the claim amendments, claims 1, 12, 13, 15, 17-21, 29 and 38-45 are now in condition for allowance.

2. **Claims Rejected Under 35 U.S.C. §103(a):**

The Examiner has rejected claims 2-11, 14, 22-28 and 30-37 under 35 U.S.C. § 103(a) as being unpatentable over *Czernielewski* in view of *Buseman*. Claims 5 and 27 have been withdrawn. Claims 9-11, 14 and 28 have been amended. Claims, 2-4, 6-8, 22-26, and 30-37 remain as originally filed. Applicant respectfully contends that the remaining claims, as amended, should be allowed in light of the following arguments:

A. *Buseman* is Moot as a Secondary Reference Under 35 U.S.C. §103(a) if *Czernielewski* has been Overcome:

As discussed above, *Czernielewski* lacks critical elements which are present in the present invention. These critical elements are similarly lacking in the *Buseman*. Accordingly, the Examiner's refusal under 35 U.S.C. §103(a) cannot be sustained on the basis of

*Czernielewski* alone, nor in combination with *Buseman* and it is respectfully requested that same be withdrawn.

B. Applicant's Date of Invention Pre-Dates *Buseman's* Effective Date as a Reference:

In addition, the Applicant's date of invention pre-dates *Buseman's* effective date as a reference. Attached as Exhibit "C" hereto, is a Declaration by Inventor of Prior Inventorship Under 37 C.F.R. 1.131 establishing an invention date at least as early as December 10, 1996. *Buseman's* effective date is January 19, 2001, more than four (4) years after that. Accordingly, *Buseman* cannot constitute prior art and it is respectfully requested that the Examiner's refusal on the basis of *Buseman* be withdrawn.

C. *Buseman* is Ineffective as a Reference Under 35 U.S.C. §103(a) as it Describes an Adhesive Patch, not a Pledget:

*Buseman* is also ineffective as a reference under 35 U.S.C. § 103(a). As acknowledged by the Examiner, *Buseman* describes a "patch." The instant application, in contrast, discloses an impregnated inert support, or pledget. A patch and a pledget are completely different.

The patch described by *Buseman* is an "adhesive patch useful for treating and preventing acne or a pimple" (See *Buseman* at column 4, line 32). The *Buseman* patch is clearly intended as a "leave-on" application mechanism for the timed transdermal release of medication.

The "pledget", or "impregnated inert support", of the instant application is non-adhesive in nature and not intended to "leave on" in a specific area of the skin. Taber's Medical Dictionary, 15th Edition, defines a "pledget" as follows: "Small , flat compress, usually of gauze or absorbent cotton, used to apply or absorb fluid, to protect, or to exclude air." The specification of the instant application repeatedly states that the delivery system of the present invention is of the "pledget" type and not a "patch."

In order to further clarify this point, all claims in the application have been amended to recite a "non-adhesive" inert support.

For the foregoing reason, and in view of the claim amendments, claims 2-4, 6-11, 14, 22-26, 28 and 30-37 are now in condition for allowance.

## CONCLUSION

Applicants submit that this Amendment and Response, if entered, places claims 1-4, 6-15, 17-26, and 28-45 in a condition for allowance and respectfully request that such action be taken by the Examiner at this time.

Should a telephone conference be necessary or desirable to assist the Examiner's evaluation of this application, a telephone call to the undersigned at (305) 448-7089 is respectfully solicited.

Dated: November 5, 2003

By: _____

Ury Fischer
USPTO Reg. No. 46,167

**LOTT & FRIEDLAND, P.A.**
Post Office Drawer 141098
Coral Gables, Florida 33114-1098

Docket No.: 19113-1-0031

Exhibit A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/765,064 | 03/25/97 | CZARNIELEWSKI | [illegible] |

12M2/0603

NORMAN H STEPNO
BURNS DOANE
SWECKER AND MATHIS
PO BOX 1404
ALEXANDRIA VA 22313-1404

| EXAMINER | |
|---|---|
| HAGHIL[illegible] | |
| ART UNIT | PAPER NUMBER |
| 1205 | 6 |

DATE MAILED: 06/03/97

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

PTO-90C (REV. 2/95) 1-File Copy

U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

## Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 08/765,054 | Czmielewski et al |
| **Examiner** | **Group Art Unit** |
| Keith MacMillan | 1205 |

☒ Responsive to communication(s) filed on *Jan 6, 1997*

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-29* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

U. S. Patent and Trademark Office
PTO-326 (Rev. 9-95) Office Action Summary Part of Paper No. 6

## DETAILED ACTION

### *Claim Rejections - 35 U.S.C. § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claim 10 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Borgman, Chemical Abstracts AN 1989:502704 (corresponding to WO 8806888.) A copy of the abstract is provided as evidence of the disclosure. Borgman teaches topical formulations of metronidazole for the treatment of skin disorders. As the disclosure meets every critical limitation of the claim, the claim is anticipated.

3. Claims 10-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Busch et al, Chemical Abstracts AN 1976:145357. Busch et al teach compositions containing both clindamycin (registry number 18323-44-9) and metronidazole (registry number 443-48-1.) Synergism resulting from the combination is also disclosed. Pharmaceutically acceptable carriers for the composition are also disclosed. Thus, the disclosure meets every critical limitation of these claims.

The recitations of intended use, and to "topical" compositions, in the claims are noted. However, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the

claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

*Claim Objections*

4. Claims 12-14, 16-17, 21-22, and 25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. These claims differ from their respective dependent claims only by recitations of intended use. As they do not contain limitations which result in structural differences in the composition, they do not further limit the claims from which they depend.

*Claim Rejections - 35 U.S.C. § 103*

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 10-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ayer et al, US Patent 4,018,918, in view of Borgman (WO 8806888, published 1988).

Ayer et al teach topical compositions which contain both clindamycin and an antiinflammatory steroid. The compositions are useful to treat a variety of skin disorders, including acne. See the abstract, which is provided as evidence of the disclosure. The claims differ in the type of antiinflammatory agent which is to be present in the composition. Ayer et al teaches a steroidal antiinflammatory; Applicants' claims call for metronidazole as the antiinflammatory. Borgman teaches that metronidazole is an excellent topical antiinflammatory, suitable for use in topical treatments of skin disorders such as acne. It would have been obvious to one of ordinary skill in the art to formulate a topical composition according to the instant claims, by substituting metronidazole rather than the steroid as the antiinflammatory. One would have been motivated to make the substitution because this prior art combination established metronidazole and the steroid shown are art equivalents. Further motivation to make the substitution comes from the very well known synergism seen in treating microbials, especially bacteriodes fragilis, when clindamycin and metronidazole are combined. See for example Busch et al, Chemical Abstracts AN 1976:145357. Still more motivation to combine these two ingredients in a topical solution comes from Deckner et al, Chemical Abstracts AN 1993:503333, published 1993. (Deckner et al corresponds to WO 9307903. A copy of the abstract is provided as evidence of this disclosure as well.) Deckner et al teach topical compositions which optionally contain both clindamycin as an antimicrobial and metronidazole as and antiinflammatory. In view of the foregoing, the claimed topical composition is rendered obvious by this combination of prior

ciation of clindamycin and metronidazole. Therefore, this reference fails to teach or suggest the claimed methods.

Claims 10-29 were further rejected under 35 U.S.C. §103 as being unpatentable over Ayer et al, U.S. Patent 4,018,918, taken in view of Borgman (WO 88/06888). Ayer et al is cited based on its disclosure pertaining to topical clindamycin preparations and their uses for treatment of skin disorders. The Examiner further notes that such compositions may comprise anti-inflammatories, in particular, steroidal anti-inflammatories. However, this reference completely fails to teach or suggest a composition comprising a combination of metronidazole and clindamycin, much less the use thereof for the treatment of inflammatory conditions.

Moreover, the deficiencies of Ayer et al are not cured by Borgman. This reference acknowledgedly teaches that metronidazole is an excellent topical anti-inflammatory which is suitable for usage in treatment of skin disorders such as acne. However, this reference contains non indication that clindamycin could potentiate the anti-inflammatory effects of this compound. Therefore, this reference also fails to teach or suggest the claimed invention.

Moreover, even assuming *arguendo* that there would have been motivation to have combined these compounds based on the fact that both had been reportedly useful for treatment of skin conditions, this rejection must be withdrawn based on the unexpected results which are achieved by the claimed invention.

As discussed above, it has been surprisingly discovered that the combination of clindamycin and metronidazole exhibit synergistic anti-inflammatory effects. Such synergism is not taught by any of the references cited by the Examiner, whether considered singularly or in combination. As discussed above, the only disclosure pertaining to synergistic activity of this combination relates to anti-microbial activity. In particular, as noted by the Examiner, it had been reported in the Busch et al Abstract that these compounds in combination exhibit greater anti-microbial activity, in particular, against bacteroides fragilis. However, such synergism would in no wise suggest that these compounds would exhibit synergistic anti-inflammatory activity. Indeed, this certainly could not have been expected given the fact that clindamycin by itself exhibits no such anti-inflammatory activity.

This absence of anti-inflammatory activity may be appreciated upon review of the results contained in Example 1. Therefore, based on the foregoing, there would have been no reason to have expected that such a combination would exhibit potent anti-inflammatory activity relative to either of these compounds used singularly. Therefore, withdrawal of the §103 rejection of Claims 10-29 based on Ayer et al taken in view of Borgman, alone, or in combination with the cited Abstracts relating to synergism, is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is re-

spectfully solicited. However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Robin L. Teskin
Registration No. 35,030

Post Office Box 1404
Alexandria, VA 22313-1404
(703) 836-6620

Date: December 3, 1997

Exhibit C

Attorney's Docket No. 19113-1-0031 *PATENT*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| In re Application of: | | |
| **KARL F. POPP** | Art Unit: | **1615** |
| Serial No. **10/044,275** | | |
| Filed: **January 10, 2002** | Examiner: | Humera N. Sheikh |
| For: **METRONIDAZOLE PLEDGET** | | |

**Assistant Commissioner for Patents**
**Washington, DC 20231**

**Declaration by Inventor of Prior Invention Under 37 C.F.R. 1.131**

I, Karl F. Popp, declare as follows:

1. This declaration is to establish completion of the invention in this application in the United States, at a date prior to January 19, 2001, the filing date of the U.S. Patent No. 6,495,158 to *Buseman, et al.* (the "Cited Reference") cited by the Examiner in the first office action (paper number 4) as a basis for rejecting claims 2-11, 14, 22-28 and 30-37 under 35 U.S.C. §103(a).

2. The person making this declaration is the inventor.

3. The following statements are submitted to establish a date of completion for the invention disclosed in the instant application at a date prior to January 19, 2001:

   a. The inventor conceived the idea of using a pledget for the delivery of a metronidazole solution including a major solvent component sometime during 1995 in the United States.

   b. As reflected in confidential corporate records of the assignee of record, the present invention, as disclosed and claimed in the present application, was

discussed at various product development meetings in which the inventor participated. The earliest of such meetings occurring at least as early as December 10, 1996 in the United States. Attached hereto as Exhibit "A" is a page from said confidential corporate records evidencing this fact.

c. As reflected in confidential corporate records of the assignee of record, the invention as disclosed and claimed in the present application was actually reduced to practice at least as early as August 14, 1997 in the United States. Attached hereto as Exhibit "B" is a page from said confidential corporate records evidencing this fact.

d. The inventor and assignee of record have diligently and continuously pursued development and refinement of the present invention in the United States from the 1995 date of conception through and beyond March 28, 2001, the date of filing of U.S. Provisional Patent Application Serial No. 60/279,382 to which priority has been claimed in the present non-provisional application.

4. From the above documentation and statements, it can be seen that the invention in this application, as disclosed and claimed in the present application, was conceived in the United States at least as early as December 10, 1996, and actually reduced to practice in the United States as early as August 14, 1997, both of which dates are earlier than the effective date of the Cited Reference.

5. This declaration is submitted with the Applicant's response to the first office action, and is for the purpose of overcoming the Examiner's rejection under 35 U.S.C. §103(a).

I declare, under penalty of the perjury laws of the United States, that all statements made herein of my own knowledge are true and that all statements made based on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Respectfully submitted,

By: _____
Karl F. Popp

Date Signed 3 February 2004

Exhibit A

Metronidazole Pledget Stage II

KFP suggested a patent be filed to cover use of metronidazole solution in pledget, pad, and dab-o-matic formats. This position would be critical if metronidazole is approved for an acne indication.

KFP File patent application for this concept.

10 December 96

After reviewing Stage I, NPC decided to move this project to Stage II.

Concept: Metronidazole solution in a pledget format would be a unique delivery system in the market place for this active. Efficacy of this delivery system in rosacea would be needed to support an NDA filing.

KFP Review patent options for this concept.

[redacted]

KFP reviewed the possible patent position for this product. [redacted]

JAJ Develop projected sales information for this product assuming a launch in [redacted]

13 February 1997

[redacted] reported potential sales for this product concept is about [redacted] for the first year.

[redacted]

NPC confirmed its interest in securing a patent on this concept.

KFP Initiate activities to file a patent application.

[redacted]

KFP [redacted]

Exhibit B

Metronidazole Pledget Stage IIIA

[redacted]

KFP Monitor patent activities.

[redacted]

23 May 97

[redacted]

KFP Monitor patent activities.

MJM reiterated marketing's interest in this project.

23 June 97

[redacted]

KFP Monitor patent activities.

25 July 97

[redacted]

Marketing interest in this product was high according to MJM as the concept would be unique for this drug.

KFP Initiate development and compatibility testing of metronidazole solutions.

KFP Move project to Stage IIIA.

14 August 97

KFP provided samples PD614-33A (aqueous base) and PD614-34A (hydroalcoholic base) for NPC evaluation and further guidance as to this product's physical attributes.

[redacted]

art. Claims 26-29 are included in this rejection because the topical route of administration and treatment of skin disorders is clear from the combination of references for the same reasons.

7. Any inquiry concerning this communication should be directed to Keith MacMillan at telephone number (703) 308-4614.

Keith MacMillan

5/28/97

Exhibit B

Patent
Attorney's Docket No. 016800-128

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COPY

| | |
|---|---|
| In re Patent Application of | |
| Janusz CZERNIELEWSKI et al | Group Art Unit: 1205 |
| Application No.: 08/765,064 | Examiner: K. MacMillan |
| Filed: March 25, 1997 | |
| For: DRUGS CONTAINING METRONIDAZOLE OR A SYNTHETIC MIXTURE OF METRONIDAZOLE AND CLINDAMYCIN | |

REPLY AND AMENDMENTS PURSUANT TO
37 C.F.R. §§1.111, 1.115 and 1.119

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action dated June 3, 1997, kindly amend the above-identified application as follows:

IN THE CLAIMS:

Kindly cancel Claims 10 through 29, and substitute the following claims therefor:

--30. A method for the treatment of inflammation, said method comprising administering a composition which comprises an effective amount of metronidazole and clindamycin and a pharmaceutically acceptable carrier therefor.

31. A method for the treatment of inflammation, said method comprising topically administering a pharmaceutical composition comprising an anti-inflammatory effective amount of metronidazole and a topical pharmaceutically acceptable carrier therefor.

32. The method of Claim 30, wherein the amount of metronidazole present in said composition ranges from about 0.01% to 5% by weight with respect to the total weight of the pharmaceutical composition.

33. The method of Claim 31, wherein the amount of metronidazole present in said composition ranges from about 0.01% to 5% by weight with respect to the total weight of the pharmaceutical composition.

34. The method of Claim 30, where said treatment of inflammation comprises treatment of a skin disease.

35. The method of Claim 33, where said treatment of inflammation comprises treatment of a skin disease.

36. The method of Claim 34, wherein said skin disease is accompanied by dermatosis.

37. The method of Claim 35, where said skin disease is accompanied by dermatosis.

38. The method according to Claim 36, wherein said dermatosis is selected from the group consisting of eczema, psoriasis, acne rosacea, acne vulgaris, ulcers, seborrhoeic dermatitides and irritations induced by chemical, physical or mechanical agents.

39. The method according to Claim 37, wherein said dermatosis is selected from the group consisting of eczema, psoriasis, acne rosacea, acne vulgaris, ulcers, seborrhoeic dermatitides and irritations induced by chemical, physical or mechanical agents.

40. The method according to Claim 30, wherein said clindamycin is present in said composition in a proportion ranging from 0.01 % to 10% by weight with respect to the total weight of the composition.

41. The method according to Claim 33, wherein said clindamycin is present in said composition in a proportion ranging from 0.01 % to 10% by weight with respect to the total weight of the composition.

42. The method according to Claim 30, wherein the overall content of the metronidazole and clindamycin mixture does not exceed 5 to 10% of the total weight of said composition.

43. The method according to Claim 31, wherein the overall content of the metronidazole and clindamycin mixture does not exceed 5 to 10% of the total weight of said composition.--

REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, Claims 10 through 29 have been cancelled in favor of new Claims 30 through 43. These amendments are made in order to expedite prosecution.

Upon entry of the subject amendments, all of the claims will be directed to a method for treating inflammation comprising administering a composition comprising an effective amount of metronidazole and clindamycin in combination with a pharmaceutically acceptable carrier, preferably by topical application. Based on the following, Applicants respectfully submit that these amendments should place this application in condition for allowance.

Turning to the Office Acti n, Applicants note at the outset that previous Claims 12-14, 16-17, 21-22, and 25 were objected to under 37 C.F.R. §1.75(c) as being of improper dependent form. The claims were indicated not to be further limiting because they only differed from the respective dependent claims by recitations of intended use. This objection should be moot based on the present amendment, which limits all of the claims to methods of treatment. Therefore, the recited intended uses comprise a proper claim limitation.

Also, all of the claims were rejected based on prior art. These rejections are respectfully traversed to the extent they may be applicable to the claims as amended. However, prior to specifically addressing the prior art, the present invention and its advantages are briefly summarized below.

The present invention generally relates to the use of metronidazole and clindamycin, in combination, for the treatment of inflammatory conditions, in particular those affecting the skin. As discussed in the subject application, metronidazole or 2-methyl-5-nitroimidazole-1-ethanol as it is also known, comprises known application for the treatment, topically, of acne rosacea as described, e.g., in U.S. Patent 4,837,378. However, while this compound effectively treats this condition, the exact mechanism which results in efficacy was poorly understood prior to the invention. It is well known, however, that this compound is an active anti-microbial

agent which is capable of killing certain anaerobic and parasitic infectious organisms.

The present inventors, quite surprisingly, have discovered that this compound exhibits potent anti-inflammatory activity, in particular when applied topically. Moreover, it has been surprisingly discovered that this compound, when combined with clindamycin, exhibits synergistic anti-inflammatory activity. This result is highly unexpected because clindamycin, like metronidazole, had recently been reported to possess activity as an antibiotic and, therefore, was commonly used in the treatment of acne by topical application thereof. However, this compound was not known to possess anti-inflammatory activity.

Based on the discovery of this synergistic activity, the present invention is directed to an effective means of treating inflammatory conditions, in particular those affecting the skin, comprising the application of a combination of metronidazole and clindamycin, e.g., by topical application to the skin. Skin diseases which may be treated with such a combination include, by way of example, eczema, psoriasis, acne rosacea, acne vulgaris, ulcers, seborrhoeic dermatitides and irritations induced by chemical, physical or mechanical agents.

The synergistic anti-inflammatory results obtained by the combination of clindamycin and metronidazole may be appreciated upon review of the results contained in Example 1. This Example compares the anti-inflammatory effects of compositions

containing metronidazole alone, clindamycin alone, in relation to a composition containing a combination of metronidazole and clindamycin, present in the same amounts by weight. Specifically, these anti-inflammatory results were evaluated in a model of inflammation comprising oedema of the ear of the mouse which was induced by topical application of arachidonic acid. According to this model, topical application of arachidonic acid causes ear inflammation characterized by the rapid development of an oedema which becomes most pronounced about an hour after application.

This response may be quantified by measuring the thickness of the ear after treatment. Thus, compounds which inhibit inflammation in this model result in a reduction of oedema characterized by reduced thickness of the ear after application. The results obtained upon application of metronidazole alone, clindamycin alone, and a combination thereof, are summarized in the Table at page 8 of the subject application. These results clearly demonstrate that the application of clindamycin alone had no statistically significant effect on inflammation. In other words, it did not inhibit inflammation. By contrast, the 2% dosage of metronidazole alone resulted in 20% inhibition of inflammation after an hour and about 36% after two hours. Moreover, quite surprisingly, the combination of metronidazole and clindamycin resulted in 46% inhibition after an hour and 63% after two hours. Quite clearly, this enhancement in anti-inflammatory activity which occurred with the combination of

clindamycin and metronidazole could not have been predicted since clindamycin alone has no apparent affect on inflammation. Therefore, the present invention constitutes a patentable invention in the art, i.e., it provides a novel and non-obvious method of treating inflammation.

Turning now to the prior art rejections, Claim 10 was rejected under §102(b) as being anticipated by Borgman. This reference teaches a topical formulation comprising metronidazole for treatment of skin disorders. This rejection is moot as a topical composition containing metronidazole is no longer claimed. Withdrawal of this rejection is therefore respectfully requested.

Claims 10-25 were further rejected under 35 U.S.C. §102(b) as being anticipated by Busch et al, Chem. Abstracts AN 1976:145357. This reference teaches a composition comprising clindamycin and metronidazole. The reference further purportedly teaches the synergistic results of such a combination. However, Applicants respectfully submit that this reference fails to teach or suggest the claimed invention as the synergism observed by Busch et al relates to an anti-bacterial effect. Essentially, the reference purports that the association of clindamycin and metronidazole had a synergistic bacteriocidal effect, in particular against bacteroides fragilis. However, this reference fails to teach or suggest the claimed method of treatment, which is directed to the inhibition of the inflammation by the application of an asso-